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Review

Using diffusion MRI to understand white matter damage and the link between brain microstructure and cognitive deficits in paediatric medulloblastoma patients

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ABSTRACT

Purpose: Survivors of medulloblastoma face a range of challenges after treatment, involving behavioural, cognitive, language and motor skills. Post-treatment outcomes are associated with structural changes within the brain resulting from both the tumour and the treatment. Diffusion magnetic resonance imaging (MRI) has been used to investigate the microstructure of the brain. In this review, we aim to summarise the literature on diffusion MRI in patients treated for medulloblastoma and discuss future directions on how diffusion imaging can be used to improve patient quality.

Method: This review summarises the current literature on medulloblastoma in children, focusing on the impact of both the tumour and its treatment on brain microstructure. We review studies where diffusion MRI has been correlated with either treatment characteristics or cognitive outcomes. We discuss the role diffusion MRI has taken in understanding the relationship between microstructural damage and cognitive and behavioural deficits.

Results: We identified 35 studies that analysed diffusion MRI changes in patients treated for medulloblastoma. The majority of these studies found significant group differences in measures of brain microstructure between patients and controls, and some of these studies showed associations between microstructure and neurocognitive outcomes, which could be influenced by patient characteristics (e.g. age), treatment, radiation dose and treatment type.

Conclusions: In future, studies would benefit from being able to separate microstructural white matter damage caused by the tumour, tumour-related complications and treatment. Additionally, advanced diffusion modelling methods can be explored to understand and describe microstructural changes to white matter.

1. Introduction

Medulloblastoma is the most common embryonal tumour of the central nervous system (CNS) and one of the most common malignant brain tumours in childhood [1]. Even though the peak age of diagnosis for medulloblastoma is 6–8 years old, it can affect children earlier in life (< 1 year of age) as well as adults [1,2]. Children are ten times more likely to be diagnosed with medulloblastoma than adults, with an incidence in children 0–9 years of 6 per million and only 0.6 per million in adults (over 19 years old) [2,3].

Medulloblastoma is classed as a World Health Organisation (WHO) Grade IV tumour [4]. These tumours arise in the posterior fossa, predominantly in the cerebellum, but can disseminate through the cerebrospinal fluid leading to metastasis elsewhere in the brain and spinal cord. Even though medulloblastoma is a high-grade tumour, studies suggest an overall 5-year survival rate of ~72% [3,5]. These higher survival rates are the result of early diagnosis, molecular and histological assessment (particularly the classification of medulloblastoma into four molecular groups), as well as treatments involving surgery, chemotherapy and radiotherapy tailored to individual risk stratification.

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Studies assessing the combination of surgical resection, craniospinal irradiation and adjuvant chemotherapy indicate a 5-year survival of up to 90% for patients with non-metastatic disease and gross total resection (GTR) and <20% for infants with metastatic disease and/or subtotal resection (STR) [6]. However, outcomes are also impacted by tumour type, traits of the cancer, age and health of the patient when diagnosed, how the tumour responds to treatment and patient risk [7–10].

Treatment for medulloblastoma negatively impacts patients' long-term quality of life, with studies showing a multitude of physical, cognitive and behavioural outcomes. Additionally, post-operative cerebellar mutism syndrome (CMS) is reported in 30% of patients following surgical tumour resection, though this has been reported to be as low as 8% and as high as 40% of patients [11–14]. This condition is characterised by a broad range of symptoms, highlighting the importance of the cerebellum in a variety of functions. After surgery, typical characteristics include a delayed onset of mutism or reduced speech and emotional lability. Other common features include hypotonia and difficulties with swallowing and oropharyngeal function [15].

Patient outcomes may be associated to changes in brain structure following treatment, which can quantified using imaging techniques such as diffusion magnetic resonance imaging (diffusion MRI). In this review, we aim to summarise the literature on diffusion imaging in patients treated for paediatric medulloblastoma. First, we discuss medulloblastoma and current treatment in Sections 1.1–1.3 and provide an overview of diffusion MRI (Section 1.4). We discuss findings of past work that used diffusion MRI to investigate microstructural changes to white matter in patients treated for medulloblastoma (Section 2) and associations between diffusion changes and characteristics of medulloblastoma, its treatment and cognitive outcomes (Sections 3 and 4). Future directions on how diffusion MRI can be used to improve patient quality of life after treatment can be found in Section 5.

1.1. Classification

WHO CNS5 [4] classifies medulloblastoma based on molecular and histological criteria to incorporate observed inter-tumour heterogeneity (i.e. 'molecularly-defined' and 'histologically-defined'). Molecular group and histological type have been found to be associated with age of tumour development, incidence of metastases and outcome. For a comprehensive overview of molecular groups and histological types, see Shih and Koeller [16], Cassia et al. [17], Northcott et al. [1] or Hovestadt et al. [18].

Molecularly-defined medulloblastoma incorporates the four principal molecular groups that have been used to characterise medulloblastoma for over a decade [4,19,20]. Classification of molecularly-defined medulloblastoma includes: (1) WNT-activated, (2) SHH-activated and *TP53*-wildtype, (3) SHH-activated and *TP53*-mutant and (4) non-WNT/non-SHH.

Histologically, medulloblastoma is characterised by small, round blue cells that are densely packed together with high mitotic activity. There are 4 histological types used to classify histologically-defined medulloblastoma, including: classic, large cell/anaplastic, desmoplastic/nodular and medulloblastoma with extensive nodularity.

1.2. Anatomy and development

Medulloblastoma originates in the cerebellum within the posterior fossa. While it is often found in the cerebellum, particularly the vermis, medulloblastoma frequently grows into the fourth ventricle, and may occupy more lateral locations within the cerebellar hemisphere [21–23].

Medulloblastomas are thought to arise from the lower rhombic lip, a region of the hindbrain of the developing brain (rhomboencephalon), which includes the medulla oblongata, the pons and the cerebellum. The cells of origin come from the lower rhombic lip progenitor cells of the dorsal brainstem which give rise to the external granule layer precursor cells before eventually migrating to the cerebellum [1]. There is evidence the different molecular groups of medulloblastoma have different origins. For example, WNT tumours are thought to arise from the precursor of mossy fibre neurons, which connect with various cells in the cerebellum. In contrast, there is evidence that Group 3 and 4 tumours have a glutamatergic lineage [6,24].

Clinical symptoms of medulloblastoma can include fatigue, nausea and vomiting, clumsiness, headaches, ataxia, difficulties with motor skills, ataxia and vision problems. School performance can be negatively affected. Hydrocephalus may develop if the tumour blocks the flow of cerebrospinal fluid near the fourth ventricle. Additionally, spinal metastases may present with back pain and lower limb symptoms [1,25]. Children suspected to have a posterior fossa tumour undergo structural MRI for diagnosis (Fig. 1). Common locations identified by MRI have previously been found to align with molecular groups [26], including the cerebellar hemisphere, cerebellar peduncle/cerebellopontine angle cistern and the midline vermis/fourth ventricle (Fig. 2).

1.3. Treatment

Treatment of medulloblastoma consists of a combination of surgical resection, chemotherapy and, in children over 3 years old, craniospinal radiation therapy.

1.3.1. Surgery

After diagnosis, the tumour is surgically resected prior to chemotherapy and/or radiation therapy. The objective is to obtain a maximal safe tumour resection. Outcomes can be impacted by the extent of tumour resection, i.e. gross-total resection (GTR; MRI can find no residual tumour), near-total resection (NTR; residual tumour is < 1.5 cm^2), or sub-total resection (> 1.5 cm^2). Traditionally, STR is associated with a higher risk and a worse outcome [10,27], but evaluation of the impact of extent of resection in a large cohort of molecularly-defined medulloblastomas has not identified a clear negative impact of residual tumour [28]. The intensity of post-operative adjuvant therapy is determined by the patient's risk status. Children under 3 years of age are not given radiotherapy and are always considered high risk. Patients with disseminated disease, subtotal resection and anaplastic features are also considered high risk.

Cerebellar mutism (CMS) is a potential complication related to surgical resection. It is more likely in children under 5 years of age with large tumours and is characterised by reduction in speech, ataxia, and emotional lability. Its precise aetiology is unknown but is likely related to injury to the efferent pathways of the cerebellum, which involve the dentate nuclei and the superior cerebellar peduncles. Typical onset of post-operative CMS occurs several days after surgery and recovery can take weeks to months with lasting effects on cognition, motor function, gait and speech [29,30].

1.3.2. Photon radiotherapy

Photon radiotherapy is administered to the entire craniospinal region after surgery as a treatment for medulloblastoma due to its tendency to spread through the cerebrospinal fluid. This includes the brain and spinal cord with a radiation boost to the primary tumour site. This method of craniospinal radiation with a focal boost to the posterior fossa or tumour site has helped improve outcomes, particularly in older children, and is the central component in medulloblastoma treatment [31–33].

According to radiation dose fractionation guidance from the Royal College of Radiologists [34], standard-risk medulloblastoma patients are recommended 23.4 Gy in 13 fractions over 2.5 weeks with a boost to the tumour bed or whole posterior fossa. High-risk patients receive either 36.0 Gy in 20 fractions over 4 weeks or 39.6 Gy in 22 fractions over 4.4 weeks, with a boost to the primary tumour site that totals 54.0–55.8 Gy.

Radiotherapy is associated with a range of neurocognitive toxicities, particularly in patients treated for paediatric brain tumours [35]. Past meta-analyses of neurocognitive effects following radiotherapy include

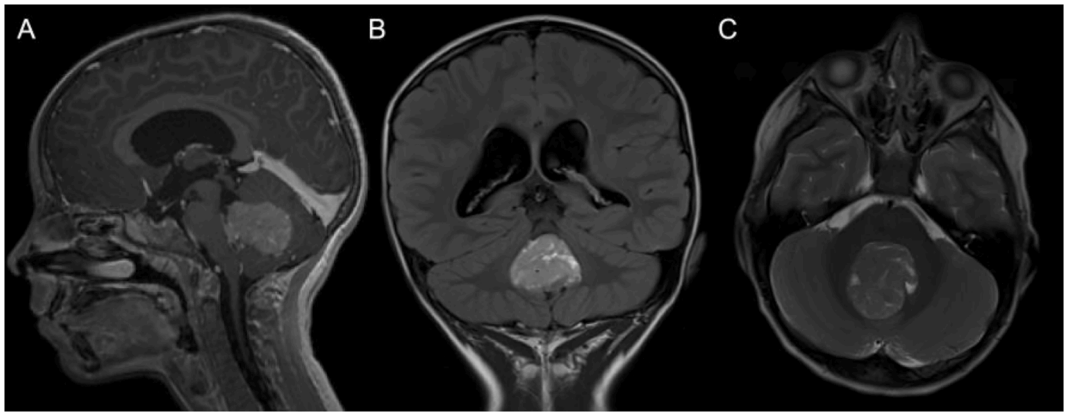

Fig. 1. Example of structural MRI scans of a paediatric patient with medulloblastoma, treated surgically at our institution, Great Ormond Street Hospital for Children. Images correspond to (A) sagittal T1-weighted post-Gadolinium, (B) coronal FLAIR (fluid attenuated inversion recovery), (C) axial T2-weighted sequences. Images taken prior to surgical resection.

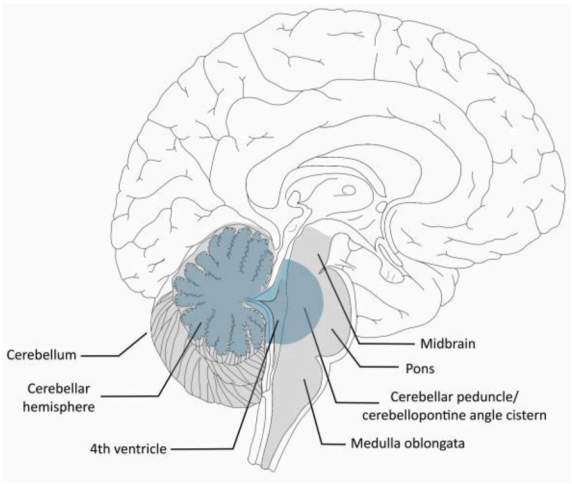

Fig. 2. Sagittal diagram of common locations medulloblastoma is found (blue), corresponding to the cerebellum and brainstem [26]. Medulloblastoma WNT corresponds to the cerebellar peduncle or cerebellopontine angle cistern in the dorsal brainstem where the brainstem and the cerebellum meet. Medulloblastoma SHH corresponds to the cerebellar hemisphere. Non-WNT/non-SHH (group 3 and group 4) medulloblastoma is often found in the midline vermis (middle of the cerebellum) and f.ourth ventricle.

deficits in verbal and nonverbal intelligence, overall cognitive ability, academic achievement, attention, executive function, language, processing speed, verbal and visual memory and visual-spatial abilities [36–38].

1.3.3. *Proton beam therapy*

An alternative to traditional photon radiotherapy is proton beam therapy. This minimises radiation exposure to healthy tissue surrounding the tumour, where there is a lower dose as the beam enters the body and no exit dose for tissues at depths greater than the Bragg peak (the location where most of the energy is deposited by the proton beam). This is important for targeting tumours near vital organs, for sparing healthy brain tissue and/or for minimising the radiation dose to the brain, particularly in paediatric patients [33,39–41].

A recent comprehensive review comparing proton beam therapy and photon radiotherapy in medulloblastoma patients from Young et al. [42] analysed the clinical outcomes of proton beam therapy after surgery in adults and children. This study found that proton beam therapy was comparable to photon radiotherapy regarding disease control, had the same or lower secondary malignancies compared to photon radiotherapy, better neurocognitive outcomes regarding IQ scores, a lower incidence of hypothyroidism and fewer acute toxicities. This is consistent with a previous study of 72 paediatric medulloblastoma patients treated with either proton beam therapy or photon radiotherapy, which found that the proton beam therapy group had better long-term outcomes (mean follow-up of 4.3 years) for global IQ, perceptual reasoning and working memory compared to the photon radiotherapy group and had more stable scores over time in all cognitive domains except processing speed Kahalley et al. [43]. However, more studies are still needed to fully understand the impact and potential benefits of proton beam therapy and how it compares to photon radiation therapy.

1.3.4. *Chemotherapy*

Chemotherapy is given after radiotherapy and has increased survival in individuals with standard and high-risk disease [7,8]. Alongside surgery and radiotherapy, it prevents the spread of medulloblastoma and recurrence. Chemotherapy is a standard practice for standard-risk medulloblastoma patients (common drugs include vincristine, lomustine and cisplatin) and more intensive chemotherapy, which may include myeloablative regimens, may be given for high-risk patients [7,8,10,34].

1.4. *Diffusion imaging*

Since medulloblastoma is primarily a paediatric tumour, most of the patients receiving treatment are young with developing brains that are highly vulnerable to injury [44]. Post-treatment outcomes are associated with long-term deficits possibly caused by alterations in brain structure. To investigate the microstructure and organisation of white matter in the brain, diffusion-weighted magnetic resonance imaging (diffusion MRI) can be used. Diffusion MRI is a non-invasive imaging technique that quantifies the motion of water molecules, which can serve as an indicator of the underlying microstructural properties of white matter in the brain.

From diffusion MRI, the apparent diffusion coefficient (ADC) can be used to quantify changes to the brain. ADC measures the overall magnitude of water diffusion in tissues [45]. This parameter is sensitive to changes in the cellularity and density of the tissue because it is sensitive to barriers that can restrict the diffusion of water. Lower ADC values in the tumour mass are associated with increased cell density.

Diffusion Tensor Imaging (DTI) is an application of diffusion MRI that models the magnitude and directionality of the diffusion of water molecules [46]. The model is based on the diffusion tensor, a symmetric 3×3 matrix of ADC values, physically representing an ellipsoid depicting the magnitude of diffusion in 3 dimensions (Fig. 3). The properties of the diffusion tensor reveal the primary directions of

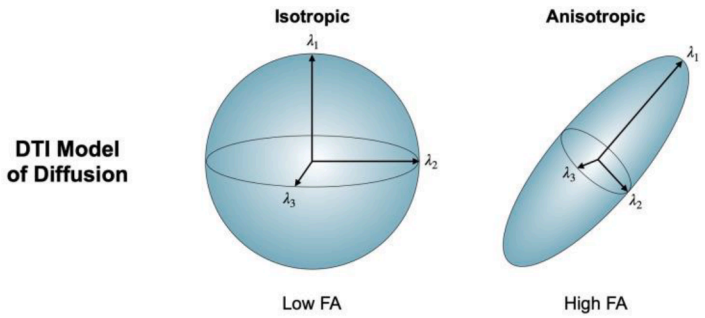

Fig. 3. Diagram of the DTI model of diffusion. FA is a measure of the directionality of water diffusion and is higher when diffusion is anisotropic. MD is the magnitude of diffusion in all directions (average of λ_1, λ_2 and λ_3). AD is the magnitude of diffusion along the principle diffusion axis (λ_1) and RD is the diffusion along the perpendicular axes (average of λ_2 and λ_3).

diffusion within the tissue, which are associated with the orientation of nerve fibres in the brain. Therefore, DTI is sensitive to the structure and orientation of white matter tracts and so can infer possible damage to the tracts, which may indicate underlying abnormalities in brain connectivity and have implications for cognition.

DTI parameters that are sensitive to microstructural tissue changes include: Fractional anisotropy (FA; measurement of the directionality of water diffusion), mean diffusivity (MD; marker of the extent of water diffusion), axial diffusivity (AD; the magnitude of diffusion parallel with the axon bundle, or the principal diffusion direction) and radial diffusivity (RD; the diffusion perpendicular to the principal diffusion direction). FA is the most common parameter used to assess white matter microstructure in DTI studies. Not only does FA indicate the orientation of white matter in the brain, but it also gives an indication about how isotropic or anisotropic the movement of water is in these regions. In white matter, diffusion is expected to be anisotropic because the movement of water tends to be along the fibre tracts.

FA can be combined with DTI parameters that measure diffusivity (MD, AD and RD) to assess properties of the white matter tracts, such as axon organisation, dispersion, density and myelination [47,48]. When white matter is damaged, this is typically reflected as a decrease in FA and increase in MD, i.e. the integrity of the white matter has changed so that the degree of anisotropy is reduced. Alternatively, increased FA has previously been observed as an indication of compression of the white matter tracts (e.g. Assaf et al. [49], Kim et al. [50], Koyama et al. [51], Ben-Sira et al. [52]). Changes in radial diffusivity (RD) and axial diffusivity (AD) can further be used to characterise the underlying nature of structural changes of white matter. Specifically, preclinical studies have linked cellular mechanisms and structural changes from DTI in animal models [48,53]. Increased RD is associated with demyelination of the axons and loss of axons, decreased AD can indicate disorganisation of axons and a combination of elevated RD with little change in AD has been associated with dysmyelination [54]. Wang et al. [55] found that DTI changes are associated with increased astrocytes and decreased myelination following high cranial radiation doses (25–30 Gy) in mouse models, indicated by decreased FA and AD alongside increased RD.

2. Diffusion MRI in medulloblastoma patients

Numerous studies have investigated the brain microstructure in individuals previously treated for medulloblastoma using diffusion MRI (Table 1). In this review, we focus on published research that used diffusion MRI (ADC) and/or DTI (FA, MD, AD or RD) to quantify white matter microstructure in patients with medulloblastoma. Past studies involved cohorts of medulloblastoma patients only as well as mixed cohorts of patients with medulloblastoma and other brain tumours or other cancers (e.g. acute lymphoblastic leukaemia).

Different image analysis techniques have been utilised to assess microstructural changes in white matter, including whole-brain analysis, voxel-level assessment, regions of interest (ROIs) and white matter tractography. These techniques can trace different aspects of white matter, from individual regions to global white matter, and identify changes between patients and control groups, which are normally matched according to age and/or sex.

Whole-brain analysis techniques focus on investigating changes to the mean diffusion parameter value (averaged across the white matter of the entire brain) in patients and characterising any global damage to brain microstructure. White matter across the brain can be explored in more detail using voxel-level assessment, which calculates DTI parameters for each voxel in white matter. This technique can then be used to quantify significant changes in DTI parameters. Tract-based spatial statistics (TBSS) [56] is a common neuroimaging analysis technique that is a voxel-based approach, which is used to detect groups or clusters of voxel-wise changes in the brain between patients and controls by projecting DTI parameters onto a common white matter skeleton (Fig. 4).

ROI studies and tractography are used to investigate the structure of specific white matter locations. In the ROI approach, DTI parameters are calculated for individual white matter regions and compared between patient and control groups to quantify structural damage to these locations. In tractography, DTI parameters are used to map and visualise individual white matter tracts in the brain. By tracking the direction of water diffusion, tractography can reconstruct the white matter tracts [57]. DTI parameters can then be calculated for the segmented tracts so that the microstructural properties can be assessed and compared between patients and controls.

Even though past medulloblastoma studies have applied different analysis techniques, a consistent finding in the majority of cross-sectional post-treatment diffusion MRI studies is a widespread reduction in FA within the white matter of individuals treated for medulloblastoma when compared to healthy controls. Notably, multiple studies have described evidence of white matter damage in regions within the cerebellum and corpus callosum [58–67]. FA serves as a marker for anisotropy, and a decrease in FA suggests that the directional restriction of water diffusion in the white matter of patients treated for paediatric medulloblastoma is less pronounced compared to controls. Additionally, several of these studies have reported elevated diffusivity (such as MD, AD or RD) in patients after treatment [60,65,66,68–71], indicating that water diffusion within the white matter is less restrained compared to control subjects.

These microstructural changes can be indicative of reduced coherence of white matter tracts, decreased fibre density, or compromised white matter integrity, including factors such as reduced axon diameter or demyelination. The extent of these DTI changes implies that both medulloblastoma and/or its treatment have a relatively global impact on the brain rather than on small, localised areas. The use of craniospinal irradiation could potentially lead to a broad disruption of the microstructural integrity of the brain.

Longitudinal studies show mixed results that are likely dependent on differences between patient groups and the response of specific white matter regions in the brain. In general, reduced FA and/or increased

Table 1
Past DTI studies involving medulloblastoma, including the DTI analysis method and type of study. The number of medulloblastoma patients are documented, including in cases with cohorts consisting of patients with different tumour types. For ROI and tractography studies, the regions of focus are included as well as details of tumour or patient characteristics and cognitive tests that were assessed in association with microstructural changes. DTI outcomes are recorded for medulloblastoma patients (after treatment unless noted otherwise).Region acronyms are: Corpus callosum (CC), cerebello-thalamo-cerebral tract (CTC), corticospinal tract (CST), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), optic radiation (OR), uncinate fasciculus (UF), anterior limb of the internal capsule (ALIC), posterior limb of the internal capsule (PLIC), proximal efferent cerebellar pathway (pECP), dentate nucleus (DN), superior cerebellar peduncle (SCP), mesencephalic tegmentum (MT), middle cerebellar peduncle (MCP), medial lemniscus (ML), spinothalamic (ST), transverse pontine fibre (TPF), dentatothalamic tract (DTT), dentato-thalamo-cortical tract (DTC), cerebro-ponto-cerebellar tract (CPC), fronto-cerebellar fibres (FCF), dentato-rubro-thalamo-cortical tract (DRTC).

Article First author	Study type	# MB patients	Region	Results
			Analysis method: Whole WM	
Khong [81]	Cross-sectional	20	Global	↓FA related to: Younger age and ↑ radiation dose
Khong [88]	Cross-sectional	12	Global	↓FA related to: ↓IQ
Aukema [62]	Cross-sectional	6	Global	↓FA
Rueckriegel [89]	Cross-sectional	18	Global	↓FA (skeletonised tracts) related to: ↓ IQ, attention shifting, processing speed
			Analysis method: Voxel-based	
Leung [58]	Cross-sectional	16	Significant clusters	↓FA: periventricular WM, CC, corona radiata and temporal, frontal and parietal lobes
Morris [93]	Cross-sectional	13	Significant clusters	↓FA in the following areas for post-op CMS patients: SCP, fornices, right angular gyrus, left superior frontal gyrus
Rueckriegel [59]	Cross-sectional	17	Significant clusters	↓FA: cerebellar midline, SCP, frontal lobes, CC (body)
Law [60]	Cross-sectional	23	Significant clusters	↓FA: CC and posterior regions of the cerebellar, occipital, parietal and temporal WM
Palmer [64]	Cross-sectional	38	Significant clusters	↓FA (widespread). No significant relationship between FA and radiation dose or risk classification. Relationship between: (1) ↓ age and ↓FA; (2) ↓ processing speed and ↓FA
Moxon-Emre [68]	Cross-sectional	34	Significant clusters	↓FA and ↑RD (widespread). Relationship between: treatment type and ↑ dose and ↓FA and↑RD, but this did not remain significant when covarying for age and post-treatment interval
Palmer [83]	Longitudinal	49	Significant clusters	No significant association between FA and risk category. Relationship between ↓ reading ability and ↓FA in: PLIC, mid cingulate, left hemisphere pons-medulla oblongata, right hemisphere pons, knee of IC and temporal, occipital and parietal WM
Glass [72]	Longitudinal	146	Significant clusters	↓FA at post-surgical baseline. ↓FA over 12–24 months after surgery in cerebellar peduncle, cingulum, IC, CST. FA improves (↑) over time in corona radiata and CC.
Partanen [73]	Longitudinal	12	Significant clusters	↓FA and ↑MD and RD at baseline during or just after radiotherapy. Over 12–36 months, MD and AD decreased in right cerebellar WM. ↑FA observed at baseline in right temporal WM
			Analysis method: ROI	
Khong [65]	Cross-sectional	9	Cerebellar hemispheres, pons, medulla oblongata, frontal periventricular WM, parietal periventricular WM, corona radiata	↓FA in: pons, medulla oblongata, cerebellar hemispheres, frontal periventricular WM, parietal periventricular WM, corona radiata. ↑MD in cerebellum. Relationship between ↓FA and ↓ age, ↑ treatment interval and ↓ school performance.
Mabbott [61]	Cross-sectional	8	CC (genu), ALIC, PLIC, frontal WM, parietal, thalamus, putamen	↓FA and ↑ADC in averaged ROIs. ↓FA in CC, PLIC, ALIC, frontal WM. ↑ADC in all ROIs. Relationship between (1) ↓IQ and ↑ADC in CC (genu), ALIC, PLIC, frontal WM, parietal WM, thalamus and putamen; (2) ↓IQ and ↓FA.
Qiu [82]	Cross-sectional	22	Frontal, parietal	↓FA in all ROIs, but more reduced in frontal WM. No relationship between radiation dose, treatment interval or age on frontal-to-parietal FA.
Aukema [62]	Cross-sectional	6	IFOF, CC (genu, splenium, body)	↓FA IFOF, CC (genu, body). Relationship between cognitive tests and ↓FA in ROIs: (1) ↓ processing speed and CC (splenium, body); (2) ↓ motor speed and right IFOF
Brinkman [90]	Cross-sectional	20	Frontal, parietal, temporal	Relationship between: (1) ↓FA in temporal lobe and ↓ cognitive fluency; (2) ↑RD in temporal and frontal lobes and ↓ cognitive flexibility; (3) ↑RD in parietal, temporal and frontal lobes and ↓ attention shifting; (4) ↓FA in parietal lobe and ↓ working memroy.
Avula [94]	Cross-sectional	1	pECP, DN, SCP, MT, MCP, vermis	Relationship between diffusion abnormalities (ADC) and post-operative CMS in pECP.
Moxon-Emre [68]	Cross-sectional	34	Temporal, occipital, frontal, parietal, posterior fossa	For higher radiation dose group: (1) ↓FA and ↑RD in all ROIs; (2) ↑MD in temporal, occipital, and posterior fossa. Reduced dose group compared to higher dose group: ↑FA and ↓RD in temporal and ↑FA in frontal. Relationship between ↑ dose and ↓ age and ↓FA (temporal, occipital).
Chua [95]	Cross-sectional	19	pECP	Relationship between restricted diffusion (ADC) in DN and higher risk of post-op CMS.
Qiu [80]	Longitudinal	2	Frontal, parietal, brainstem	↓FA in frontal and parietal WM following radiotherapy and ↑FA in brainstem. Relationship between ↓FA and ↑ radiation dose up to 45 Gy. Frontal WM had larger ↓FA than parietal WM.

(*continued on next page*)

Table 1 (*continued*)

Article First author	Study type	# MB patients	Region	Results
Hua [74]	Longitudinal	7	CST (pons), ML, ST, pons	There were 3 patterns in FA over a period of 5 years observed in patients: (1) FA is normal-developing, (2) an initial ↓FA with subsequent recovery or (3) ↓FA without a complete recovery. ML/ST tract showed better recovery than CST. No relationship between radiation dose and FA.
Uh [79]	Longitudinal	42	CST, ML, TPF, MCP	↓FA in pons, TPF, MCP. ↓AD and RD in MCP, midbrain, CST, ML. ↓AD and ↑RD in TPF. Relationship between ↓AD in CST and ↑ radiation dose.
Perreault [26]	Longitudinal	7	DTT	↓FA in DN and SCP between 1–7 days after surgery and 1–6 months later before returning to baseline at > 6 months post-surgery. ↑MD in SCP and cerebellar WM between 1–7 days after surgery and 1–6 months later before returning to baseline at > 6 months post-surgery. ↓MD in DN at all time periods. No relationship found between FA or MD and treatment type, motor skills or post-op CMS.
McEvoy [85]	Longitudinal	14	SCP, MCP, cerebellar WM	↓FA in SCP and left cerebellar WM in immediate post-operative scan and at 1 year after surgery for post-op CMS patients. ↓AD after surgery in right SCP in post-op CMS. Relationship between (1) ↓FA in SCP and ↓ age; (2) ↑MD and RD in the left SCP and post-op CMS. No significant correlation found between tumour size or location and FA in SCP
Glass [72]	Longitudinal	146	Frontal lobes	↓FA and ↑AD in post-surgical baseline. Over time (12–24 months), FA increased and AD and RD decreased. At post-surgical baseline, ↓FA in frontal WM in high-risk group compared to low-risk. Relationship between: (1) ↓FA (frontal WM) at baseline and ↓ attention and ↓ processing speed at 36 months post-surgery.
Vedantam [92]	Longitudinal	9	SCP (DTC), MCP (CPC)	Relationship between: (1) ataxia and ↓FA in left SCP in follow-up scans (up to 24 months after surgery), (2) ↓FA in left SCP in post-operative time point (within 48 h after surgery) and post-op CMS. No significant DTI changes were found in pre-surgical imaging for patients with and without post-op CMS.
			Analysis method: Tractography	
Mabbott [61]	Cross-sectional	2	CC	Evidence that fibre tracts were thicker and more complex in controls than patients, indicating that ↓FA from ROI analysis was due to differences in axonal and WM integrity.
Caan [63]	Cross-sectional	5	CC	↓FA in CC (genu, body, splenium)
Law [60]	Cross-sectional	23	CTC	↓FA and ↑RD in the cerebellar region of CTC. Relationship between (1) ↑ tumour size and ↑MD and AD for right CTC; (2) ↑ post-treatment interval and ↓FA and ↑MD and RD for right CTC; (3) ↓ age and ↑AD in left CTC; (4) ↓ working memory and ↓FA in right CTC
Law [69]	Cross-sectional	14	CTC	↑MD, AD and RD in right cerebellar region of CTC in post-op CMS patients.
Soelva [67]	Cross-sectional	8	FCF	↓FA in frontal WM and SCP of FCF in patients with and without post-op CMS.
Ojemann [96]	Cross-sectional	7	DT	In patients who developed post-op CMS, the SCP could not be discerned using tractography in post- or pre-operative images. The SCP was visible on patients who did not developed post-op CMS.
Riggs [91]	Cross-sectional	19	UF	↓FA in the UF. Relationship between ↓FA in left UF and ↓ memory.
Law [66]	Cross-sectional	34	CPC, CTC	↓FA and ↑MD in CTC and CPC, ↑RD in CPC and ↑AD in CTC. Relationship between FA in CPC and CTC and age during early and late adolescence.
Scantlebury [71]	Cross-sectional	31	ILF, IFOF, UF	↓FA in left OR and right IFOF. ↑MD and RD in OR, IFOF and right ILF. ↑AD in right OR. Relationship between ↓ processing speed and: (1) ↓FA of OR; (2) ↑MD, AD and RD of the right OR; (3) ↑MD and RD of left UF. The treatment type was able to predict RD in the right OR and processing speed.
Law [70]	Cross-sectional	24	CPC, CTC	↑MD, AD and RD in the CTC. ↑MD and RD in left CPC. Relationship between ↑RD of the left CTC and working memory.
Oh [84]	Cross-sectional	9	CPC, CTC	No FA difference in CTC or CPC (on average of 3.6 years after surgery).
Partanen [73]	Longitudinal	12	CST, IFOF, ILF, OR, UF	↑AD in CST and ↑MD in right CST at baseline just after or during radiotherapy. Over 12–36 months, MD in right CST decreased. Relationship between: (1) ↓FA (right IFOF) at baseline and ↓ processing speed over time; (2) ↑MD (right CST) and ↓ perceptual reasoning
Toescu [75]	Longitudinal	28	DRTC (SCP)	↓FA in distal third of left SCP at pre-operative scan. Post-operatively, ↓FA in distal left SCP which was more pronounced in the post-op CMS group compared to patients without post-op CMS.

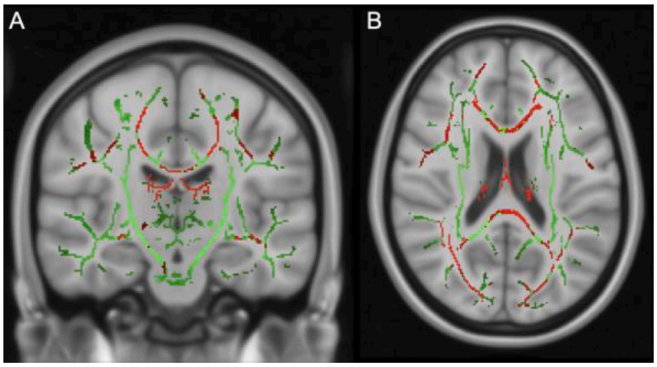

Fig. 4. Example of a TBSS analysis of a fractional anisotropy (FA) map (A, coronal view; B, axial view). Images are processed from a group of 4 patients with posterior fossa tumours at our institution (including the medulloblastoma patient in Fig. 1) against 12 age- and sex-matched controls after surgery. Green voxels denote the white matter skeleton from the TBSS analysis where there has been no change in FA between the patient and control groups. Red voxels denote areas with significantly decreased FA values ($p < 0.05$). TBSS results have been projected onto a T1-weighted template image (MNI152 standard-space; Montreal Neurological Institute, .McGill, Canada).

diffusivity is common at a baseline scan (e.g. just after surgery or after all treatment) in patients treated for medulloblastoma compared to healthy controls [72–75]. However, subsequent recovery or damage to these regions over time differs between studies. In the voxel-wise TBSS analysis from Glass et al. [72] of 146 medulloblastoma survivors, damage to the corpus callosum and corona radiata appeared to recover over time as evidenced by an increase in FA from the post-surgical baseline scan to post-treatment scans at 12 to 24 months afterwards. Other regions, including the cerebellar peduncle, internal capsule, corticospinal tract and cingulum, continued to demonstrate white matter damage by decreased FA. This can be compared to Perreault et al. [76], where certain regions, such as the dentate nuclei and superior cerebellar peduncle, initially exhibited damage shortly after surgery and treatment, as indicated by a decrease in FA. These regions showed signs of recovery with increased FA at 6 months or more after surgery. However, there is some evidence that the dentate nuclei continued to show damage over time, with decreased MD after surgery (over a 6 to 12 month period) alongside volume loss over the same time period, which was indicative of atrophy.

These previous longitudinal studies suggest that medulloblastoma and/or its treatment potentially has a long-lasting impact on brain microstructure. The nature of these microstructural changes across white matter regions is likely not uniform for paediatric medulloblastoma patients because the brain is developing and different regions will be more susceptible to damage from the tumour or radiation treatment than others [44,77,78]. The brain tumour and treatment type as well as the characteristics of patients, such as age, may all be contributing factors to the nature of microstructural changes in white matter. Further studies are needed to explore these associations and better understand the implications on the developing brain.

3. Associations between diffusion parameters and tumour and treatment characteristics

Past studies have probed for possible associations between diffusion changes in brain microstructure and characteristics of medulloblastoma and treatment. This includes tumour size, risk categorisation (standard- or high-risk), treatment type (e.g. surgery with craniospinal radiation and a boost to the posterior fossa or tumour bed, surgery only, surgery with focal radiation, etc), radiation dose, treatment interval (time elapsed since radiation) and patient age at diagnosis and treatment. There are noticeable discrepancies among studies concerning the relationship between microstructure and medulloblastoma characteristics.

Multiple studies have reported that factors, such as treatment type, radiation dose and time interval, significantly affect brain microstructure as indicated by decreased FA and/or increased diffusivity [60,65,68,71,79,80]. There is evidence that these effects between radiation dose and microstructural changes are region dependent, e.g. the corticospinal tract in Uh et al. [79] and frontal lobes in Qiu et al. [80] have specifically been found to show sensitivity to radiation dose over other regions. However, individual brain regions and/or DTI parameters that indicate microstructural white matter damage are not consistent between studies. Other studies did not find a significant association between DTI parameters in numerous white matter regions, including the corticospinal tract or frontal lobes [26,64,74,81–84]. Low patient numbers, differences in regional focus and technique or white matter recovery at longer time intervals may contribute to inconclusive findings across these studies.

Similarly, studies of tumour characteristics, such as size or risk (e.g. standard-risk and high-risk), yielded mixed results. Tumour size was correlated to increased MD and AD in the right cerebello-thalamo-cerebral (CTC) pathway in Law et al. [60], which connects the cerebellum to the frontal cortex and supports working memory function. This pathway includes the deep cerebellar nuclei, thalamic nuclei, cerebellar peduncles and midbrain. This association could indicate that white matter is being damaged prior to radiation treatment from the spread of the tumour through the white matter as well as compression against the surrounding area. Conversely, in a separate study by McEvoy et al. [85] involving the same pathway, FA in the superior cerebellar peduncle was not found to be correlated to tumour size when comparing patients with different post-operative language outcomes (i.e. verbally intact, mild language impairment and posterior fossa syndrome). There were also no significant group differences in the ratio of the tumour portion in the superior versus inferior cerebellum. Regarding patient risk classification (high- and standard-risk), Glass et al. [72] found that classification could be associated with bilateral frontal white matter abnormality, where FA was found to be significantly lower in the high-risk group compared to the standard-risk group just after surgery (with no changes in diffusivity parameters RD and AD). However, DTI parameters over time (up to 3 years after surgery) were not statistically different between patient groups, indicating that the microstructural damage to supratentorial white matter only affected patients at an early stage prior to treatment.

Age is known to affect diffusion parameters in the developing brain in newborns and children, specifically resulting in increased FA and decreased diffusivity in white matter with age [86,87]. Developmental changes that can contribute to alterations in diffusion include pre-myelination, myelination, reduced water in the brain, increased diameter in white matter fibres, change in the compactness of fibre tracts and a decrease in extra-axonal spaces due to the maturation of white matter. In relation to the impact of medulloblastoma and its treatment on the developing brain, younger age at time of diagnosis or treatment was associated with decreased FA and/or increased diffusivity parameters AD and RD post-treatment [60,64,65,68,81,85]. Age appeared to play a role alongside treatment received, specifically in cases where treatments adversely impacted particular age groups. In a voxel-wise study of DTI parameters across brain white matter, Moxon-Emre et al. [68] identified that FA values decreased in areas corresponding to the occipital and temporal white matter with increasing radiation dose and younger age at diagnosis (i.e. less white matter damage in older children). Predictive modelling indicated that both age and radiation dose performed better in estimating FA in the temporal region while radiation dose served as a stronger predictor for FA in the occipital region. Similarly in the cerebro-ponto-cerebellar and cerebello-thalamo-cerebral pathways, Law et al. [66] found a relationship between FA and treatment age for survivors of medulloblastoma. However, this association was only evidenced during mid-to-late adolescence and absent from the childhood age group.

It is possible that a complex interplay of risk factors, including treatment type, radiation dose, and age, may interact to influence long-term microstructural outcomes in patients treated for paediatric medulloblastoma, warranting further in-depth analysis.

4. Associations between diffusion MRI measures and neurocognitive outcomes

Brain microstructure is significantly associated with numerous cognitive outcomes for medulloblastoma as well as post-operative CMS. Past studies have found that poorer cognitive outcomes are correlated with decreased FA (and/or increased diffusivity) in white matter across the whole brain, supratentorial white matter, widespread clusters across the brain and in specific white matter tracts and regions. Decreased IQ was associated with elevated ADC [61] and reduced FA [61,88,89] throughout white matter. Reduced FA in regions throughout the brain were also correlated to poorer school performance [65], cognitive fluency [90], reduced attention [72], reduced attention shifting ability [89,90], reduced working memory [60,90], processing speed [62,64,71–73,89], impaired memory function [91], lower reading ability [83], reduced visual matching abilities [64], impaired motor skills [62,92] and post-operative CMS [75,85,92,93]. Additionally, diffusion (ADC) abnormalities have been associated with post-operative CMS [94,95] as well as the inability to discern the superior cerebellar peduncle using tractography at a post-operative or pre-operative time point [96].

Age appears to have a statistically significant effect on the association between the structural integrity of white matter and cognitive outcomes, though the degree of this effect is not clear (e.g. processing speed and post-operative CMS symptoms in Palmer et al. [64] and McEvoy et al. [85]). Age is associated with changes in brain development, functional abilities and sensitivity to radiation related damage. Damage to brain tissue can disrupt or delay normal developmental processes as well as the maturation of white matter and its pathways [83,97]. Further work will help to clarify the nature of these associations and the interactions between the tumour, tumour-related complications, treatment characteristics, outcomes, age and structural changes within the brain.

Observed microstructural changes from diffusion MRI may also be used as biomarkers for predicting the cognitive impact of medulloblastoma treatment, which can inform post-treatment interventions that benefit patient quality of life. In a meta-analysis investigating the relationship between microstructural changes (DTI parameters) and cognitive outcomes in patients receiving paediatric radiotherapy, Voon et al. [98] analysed 15 studies and 603 patients, including survivors of medulloblastoma. The study demonstrated that there was a significant correlation between white matter integrity, as indicated by FA, and cognition, where decreased FA was consistently associated with poorer cognitive outcomes. In particular, FA in the genu of the corpus callosum was identified to be a potential biomarker of treatment-related cognitive outcomes.

5. Future directions

There are numerous opportunities to gain a deeper understanding of how medulloblastoma and its treatment affect brain microstructure and neurocogntive outcomes. While some of the studies in this review employed a longitudinal approach, which is valuable for investigating the long-term impact of the tumour and its treatment on brain microstructure, there is a need to disentangle the effects of medulloblastoma from those attributed to treatment. It is likely that neurocognitive outcomes are the result of a complex interaction between damage caused by the tumour, tumour-related complications and treatment.

Past work has attempted to separate the effects of medulloblastoma from treatment by investigating the impact of tumour size or location in addition to different treatment types or radiation doses on brain microstructure and cognitive outcomes [26,60,64,65,68,71,72,74,79–83,85]. This process is difficult because characteristics of the tumour and the resulting treatment are highly interconnected, e.g. patients with more serious tumour presentations tend to receive more aggressive treatments.

Several studies have found potential damage to white matter prior to radiation treatment. In Glass et al. [72], medulloblastoma survivors had widespread decreased FA in white matter compared to healthy controls in baseline imaging after surgery but prior to the start of chemotherapy or radiotherapy. It is possible this damage has an impact on neurocognitive outcomes, as evidenced by a correlation in the lower FA in baseline scans and decreased performance in processing speed and attention 36 months after the scans. Similarly, while there are no significant FA differences between pre-operative imaging in patients with and without symptoms of post-operative CMS (originally denoted as posterior fossa syndrome or PFS) in McEvoy et al. [85], there is evidence of more white matter damage in the left superior cerebellar peduncle in CMS patients (increased diffusivity) before surgery. This indicates the tumour itself is involved in the observed microstructural changes to white matter. Law et al. [60] also found an association between tumour size and increased diffusivity in the right CTC pathway, which suggests that the tumour may damage white matter prior to treatment.

Quantifying the impact of the tumour and related pre-treatment complications can lead to a better understanding of the impact of radiation treatment on the brain as well as the possible cumulative damage to white matter over time. Tumour size or location may not be the only factors contributing to pre-surgical and pre-adjuvant therapy (i.e. after surgery but prior to chemotherapy and/or radiotherapy) white matter damage. The location of medulloblastoma and all posterior fossa tumours near the fourth ventricle makes it likely for patients to develop hydrocephalus and exhibit enlarged ventricles [99]. Studies on hydrocephalus [49–52] suggest that periventricular white matter (i.e. white matter near the ventricles) is associated with microstructural changes, as indicated by an increase in FA (due to compression) or decrease in FA (due to underlying damage). It is possible that damage to white matter from medulloblastoma and related complications combined with the effects of radiation could lead to poorer neurocognitive outcomes.

Future studies can consider investigating medulloblastoma patients with similar tumour presentation who received different treatment strategies, which may differ due to changes in treatment protocols over time. Proton beam therapy has become a part of medulloblastoma treatment relatively recently, particularly for standard-risk patients, due to its ability to spare healthy tissue surrounding the tumour in comparison to traditional photon radiation therapies [42]. Comparisons between brain microstructure and neurocognitive outcomes in relation to photon and proton beam therapies in medulloblastoma patients can be undertaken to better understand how different treatments affect the structure and function of the brain. In Mash et al. [100], preliminary evidence of brain tumour patients (primarily low-grade gliomas, embryonal tumours and ependymomas) indicates that there are more white matter changes and poorer cognitive outcomes for patients who received photon therapy compared to individuals who received proton beam therapy. This could translate to better outcomes for medulloblastoma patients treated by proton beam therapy, especially since proton beam therapy is expected to spare healthy tissue from the radiation boost to the tumour site. Radiation dose distribution maps that are used in individual radiotherapy planning can be registered onto diffusion MRI for direct comparisons between regional radiation doses and microstructural changes in white matter.

As described in Section 1.1, medulloblastoma is classified based on its four principal molecular groups and histological types to account for tumour heterogeneity. The molecular groups and histological types of medulloblastoma have different associated prognoses. Another area of future research could investigate the microstructural brain outcomes for different medulloblastoma classifications separately. This could contribute to better understanding of how the tumour and treatment

impacts brain structure and quality of life in medulloblastoma patients.

This review has highlighted past work on understanding the brain microstructure of medulloblastoma patients using diffusion MRI techniques, specifically ADC and DTI parameters. While the diffusion tensor is a valuable tool for estimating and modelling water diffusion in the brain, the model has well recognised limitations, i.e. it is not able to account for complex white matter tract arrangements. Specifically, the diffusion tensor model is unable to resolve crossing white matter fibres. This method also cannot identify if changes to diffusion parameters, such as FA, are the result of changes to the coherence of the white matter tracts, i.e. the extent to which the bundles of axons are aligned with one another, or properties of the tracts themselves, such as axon density, diameter or myelination. Alternative diffusion models have been developed to address some of these issues and it would be beneficial if future studies incorporated these advanced methods to shed further light on the microstructural underpinnings to the brain white matter in patients as well as act as a comparison to the DTI technique. Constrained spherical deconvolution [101] can better resolve crossing fibres, which could be useful for improving tract reconstructions in tractography.

Another advanced method of modelling diffusion MRI data is Neurite Orientation Dispersion Diffusion Imaging (NODDI), which enables measurement of axon density and dispersion [102]. With the ability to account for the coherence of fibre tracts, NODDI is able to disentangle the effects of axon density from axon dispersion, both factors contributing to FA. Whilst investigations using models such as NODDI in medulloblastoma patients have yet to appear in the literature, future studies could make use of this more advanced model or similar advanced models (e.g. spherical means technique; [103]) to generate a more comprehensive picture of brain microstructural changes in brain tumour patients and how they relate to outcome.

6. Summary and conclusions

In summary, we identified 35 studies that analysed diffusion MRI changes in patients treated for paediatric medulloblastoma. The majority of these studies show significant group differences in measures of brain microstructure (primarily FA and/or ADC) between posterior fossa brain tumour patients and controls. Some of these studies showed associations between white matter microstructure and neurocognitive outcomes, which may be influenced by patient characteristics, such as age, or treatment, radiation dose or treatment type. Since diffusion MRI techniques focus on white matter, this suggests that medulloblastoma and its treatment impacts the structural connectivity of the brain and that these microstructural changes are associated with neurocognitive outcomes. Future studies would benefit from being able to separate damage to white matter caused by the tumour, tumour-related complications and treatment as well as exploring more recent advanced diffusion modelling methods to further understand and describe microstructural changes to white matter in medulloblastoma patients. By studying microstructural damage to white matter, diffusion MRI has the potential to optimise both surgical and radiotherapy treatment approaches to improve patient outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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